REMARKS

Claims 28-37 are pending after entry of this paper. Claims 28, 29 and 33 have been rejected. Claims 34-37 have been newly added. Claims 30-32 have been withdrawn and claims 1-27 have been previously cancelled without prejudice. pplicants reserve the right to pursue withdrawn and cancelled claims in a divisional or continuing application.

Claims 33 have been amended to maintain broad terms, while what the applicants believe to be the narrower terms are presented in the newly added claims 34-37. Support may be found throughout the instant specification. No new matter has been introduced by these amendments. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Furthermore, applicants would like to thank the Examiner for conducting an interview on September 1, 2009. The Examiner and Applicants' attorney discussed the application and potential responses to the pending Office Action. Applicants have drafted this response in view of the points discussed during the interview.

Response to Rejections under 35 U.S.C. §112

Claim 33 have been rejected under 35 U.S.C. §112, second paragraph for indefiniteness. Specifically, the Examiner contends that the claim recites overlapping terms. Applicants respectfully disagreed.

However, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have deleted the overlapping terms in claim 33 and added new claims 34-37 to recite the narrower terms. Applicants respectfully request

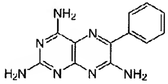
reconsideration and withdrawal of the §112, second paragraph, in light of this amendment to the claims.

Response to Rejections under 35 U.S.C. §103

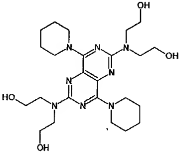
Claims 28, 29, and 33 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Yurugi et al., *Chem. Pharm. Bull.*, vol. 20, pages 1513-1521 **(1972)** (hereinafter "Yurugi") in view of WO 02/09681 to Zhilov ("Zhilov"), and further in view of Goldenberg, *Clinical Therapeutics*, vol. 20, pages 1033-1048 **(1998)** ("Goldenberg"). Specifically, the Patent Office maintains that Yurugi teaches a 2-Substituted-5,6,7,8-tetrahydropyrimido[4,5-d]pyridazine-5,8-dione (6) having a variety of substitutions for R. The Patent Office further contends that "[a]mong tetraazanaphthalene derivatives a number of pharmacologically active compounds have been known and employed as diuretic agents and cardio-vasodilators." (Office Action; p. 5). The Patent Office acknowledges that Yurugi is silent about the pharmacologically acceptable salts or treating sexual disorders/dysfunctions, however allegedly "these deficiencies would have been obvious in view of the teachings of Zhilov and Goldberg [sic]" because Zhilov teaches a variety of pharmacologically acceptable salts and Goldenberg teaches that vasodilators are important in treating male erectile dysfunction. *Id.* at p. 6. Applicants respectfully disagree with the conclusion arrived by the Patent Office based on the following grounds.

As an initial matter, applicants wish to remind the Patent Office that the presently pending claims are not directed to a composition but rather directed to a method of treating diseases caused by disorders of nitrergic system and/or dopaminergic system by administration of the disclosed compound(s).

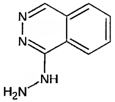
Yurugi describes three pharmacologically active compounds based on the N-heterocyclic ring structure: (1) 2-phenyl-3,5,7-triaminopteridine (triamterene) as a diuretic agent, (2) 2,7-Bis(2-hydroxyethyl)amino-4,8-dipiperidinopyrimido-[5,4-d]pyrimidine (dipyridamol) as a cardio-vasodilator, and (3) 1-hydrazinophthalazine (hydralazine) as a hypotensive agent.



(1)

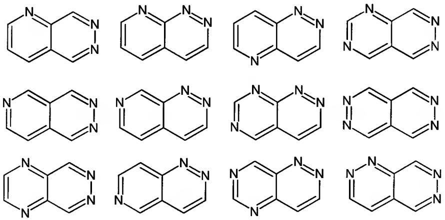


(2)



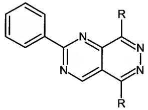
(3)

Yurugi also states, as cited by the Patent Office, that "[w]e have been interested in the syntheses of the pyridazine-containing tri- and tetraazanaphthalene derivatives . . . because [compound (3)] is well known as hypotensive agent." Applicants wish to draw the Patent Office's attention to the fact that the pyridazine-containing tri- and tetraazanaphthalene derivatives incorporate any compound that has a basic naphthalene (two fused benzene rings) with at least two adjacent nitrogen atoms (pyridazine) and one or two additional nitrogen atoms within the rings. Here are some examples of such compounds (also see charts 3-9 of Yurugi) that with various possible



side-chains/groups proposed by Yurugi (e.g., see Table II or III) may account for many millions of possible chemical compounds.

Such plethora of possibilities would send a skilled artisan on a fishing expedition to identify the possible hypotensive agents with no indication as to any finite number of identified, predictable solutions, with a reasonable expectation of success. KSR, 550 U.S. at ___, 82 USPQ2d at 1397 (see MPEP 2143). Merely a possibility that some of these compounds may be capable of acting as hypotensive agents out of an exceeding number of various compounds does not established a structure/function relationship to support the alleged *prima facie* case of obviousness. In fact, the Yurugi reference merely deals with a method of synthesis of various N-heterocyclic compounds, such as the synthesis of 2-Substituted-5,6,7,8-tetrahydropyrimido[4,5-d]pyridazine-5,8-dione, 2,4-diphenyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyridazine-5,8-dione, 2-amino-4,6-diphenyl-1,3-dihydropyrrolo[3,4-d]pyridazine-1,3-dione and many others (see Charts 3-9 of Yurugi), and does not identify or suggest that any of such compounds may have a pharmacological function, *i.e.*, a hypotensive function or more specifically an effect on the disorders of nitrergic system and/or dopaminergic system. In fact, in a subsequent work, Yurugi identified several pyridazine-containing tetraazanaphthalene derivatives such as dissubstituted 2-aryl-5,8-dichloropyrimido [4,5-d] pyridazine compounds that show diuretic activity. (see Yurugi et al., "Studies on the Syntheses of N-Heterocyclic Compounds. VII. 2-Aryl-5,8-disubstitutedpyrimido [4,5-d] pyridazine," *Chemical & pharmaceutical bulletin* 20(7), 1528-1535, 1972; attached herewith).



Such subsequent finding of Yurugi would provide no suggestion that these compounds may be used in erectile dysfunction, and in fact, would lead away from using these compounds in erectile dysfunction because it has been known in the art that many diuretics, e.g., hydrochlorothiazide, cause erectile dysfunction. Thus, while the applicants do not dispute that "a *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities," (Office Action; p. 7), such case was not established here. Therefore, for at least the above-recited reasons, the instant method of treating diseases caused by disorders of nitrergic system and/or dopaminergic system is not made obvious by Yurugi, and the shortcomings of Yurugi are not compensated by the disclosure of Zhilov and/or Goldenberg.

Furthermore, the Patent Office concludes that since hydralazine is a hypotensive agent (Yurugi) and a vasodilator, and since Goldenberg teaches that vasodilators are important in treating male erectile dysfunction, it would have been obvious to a skilled artisan a the time of the invention "to treat sexual disorders/sexual dysfunctions employing the compounds of Yurugi." (Office Action, p. 7). Following the logic of the Patent Office, 1-hydralazine should be a potent agent to treat sexual disorders/dysfunctions. However, on the contrary, while 1-hydralazine is used to treat hypertension, it has minimal if any effect in treating sexual disorders. In other words, merely because a compound a vasodilator, does not mean it can be used to treat an erectile dysfunction. Goldenberg teaches that the erectile dysfunction may be caused by an impaired arterial blood flow, the interruption of the nerve impulses, hormonal imbalance and the increased concentration of catecholamine in the blood due to stress and anxiety. (Goldenberg, p. 1033-1034). Goldenberg also teaches that vasodilators are important to treat erectile dysfunction by directly relaxing the smooth muscle of the *corpora cavernosa* (the penile tissue) and the

cavernosa arteries. *Id.* at 1035. Applicants respectfully assert that one skilled in the art would not and could not consider the method of directly relaxing corporal smooth muscles to be identical or similar to the claimed method of treating the disorders of the nitrergic system and/or dopaminergic systems. These are two completely different modes of action.

Even assuming for an argument sake that Yurugi, Zhilov and Goldenberg could be combined, such combination would not result in the claimed method. It would result, as noted above, in using the Yurugi compounds as the direct corporal smooth muscle relaxant and not as an agent to treat disorders of the nitrergic system and/or dopaminergic systems. Therefore, a skilled artisan would not be able to arrive at the claimed invention based on the disclosure of the Yurugi in combination with Zhilov and Goldenberg as suggested by the Patent Office.

Finally, in addition to above-provided arguments of non-obviousness, applicants also respectfully submit herewith a declaration under 37 CFR §1.132 by Mr. Zhilov (one of the inventors) to demonstrate the unexpected results of the claimed method in treating the disorders associated with the dysfunction of the nitrergic system and/or dopaminergic systems such as the erectile dysfunction as compared to Tadalafil (sold under the brand name Cialis®). Tadalafil is a commonly used medication to treat the erectile dysfunction by inhibiting PDE5 enzyme that breaks down the cyclic GMP produced in a corporal smooth muscle tissue (penile tissue). Tadalafil also causes a vasodilatation. On the other hand, the compounds tested in accordance with the present invention act upon the dopaminergic and nitrergic systems of the brain and do not as diuretic agents or cardiovasodilators. The results of a comparative study show that the compounds used in accordance with the claimed invention as compared to Tadalafil produced

shorter latent period of the first erection, greater number of erections, and shorter time between erections.

Therefore, in light of the arguments presented above and the declaration of the inventor, neither the combination of, nor Yurugi, Zhilov and Goldenberg alone, suggests the claimed method of treating disorders of the nitrergic system and/or dopaminergic systems using the compounds described in presently pending claim 28. Applicants respectfully assert that the combination of Yurugi, Zhilov and Goldenberg does not make obvious the claimed invention. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §103(a) rejection of claim 28, 29 and 33 in view of the aforementioned remarks and the declaration of the invention.

Dependent Claims

The applicants have not independently addressed all of the rejections of the dependent claims. The applicants submit that for at least similar reasons as to why independent claim(s) 29 and 33 from which all of the dependent claims 28 depend are believed allowable as discussed *supra*, the dependent claims are also allowable. The applicants however, reserve the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application. Favorable action by the Examiner is earnestly solicited. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-4827**, Order No. 1004398.002US.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-4827**, Order No. 1004398.002US.

Respectfully submitted,
Locke Lord Bissell & Liddell LLP

Dated: April 5, 2010

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[Chem. Pharm. Bull. 20(7)1528–1535(1972)] UDC 547.852' 853.3.04

Studies on the Syntheses of N-Heterocyclic Compounds. VII.[1] 2-Aryl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine

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(Received January 31, 1972)

When 2-aryl-5,8-dichloropyrimido[4,5-*d*]pyridazine (**1**) was reacted with a variety of nucleophiles, such as amines, sodium methoxide, sodium azide, sodium sulfide *etc.*, 5,8-disubstituted compounds (**5**) were obtained. Treatment of 2-phenyl-5-chloro-8-morpholinopyrimido[4,5-*d*]pyridazine (**9**, $^{R}_{R}\rangle$N: morpholino) or 2-phenyl-5-morpholino-8-chloropyrimido[4,5-*d*]pyridazine (**10**, $^{R}_{R}\rangle$N: morpholino) with nucleophiles gave the corresponding products with a different kind of substituents at 5- and 8-position (**12** and **13**). The phenyl group at 2-position seems to accelerate the substitution at position 5 and 8. The reaction of 2-phenyl-5,8-bis(substituted thio)pyrimido[4,5-*d*]pyridazine (**5**) with chlorine afforded the dichloride (**1**, Ar: phenyl). Among the synthesized disbstituted compounds, **5v**, **5h**, **5i**, **5j**, **5k**, **5m**, **5C**, **5E**, **5F**, **5K**, **5M** and **5O** showed diuretic activity.

In the preceding paper[1] nucleophilic mono-substitution of 2-aryl-5,8-dichloropyrimido-[4,5-*d*]pyridazine (**1**)[3] has been reported. This paper deals with the disubstitution reaction of **1** with various nucleophiles.

In regard to the nucleophilic substitution of 1,4-dichloropyridazine system (**2**), several papers are found in the literatures,[4–8] but none of them have succeeded in the disubstitution by aliphatic amine. On the other hand, the disubstitution of the dichloride (**2**) with arylamines occurs smoothly. According to Castle, *et al.*,[8] the difference in the reactivity between aliphatic and aromatic amines with 5,8-dichloropyrazino[2,3-*d*]pyridazine (**3**) can be explained on the basis of the higher electron donating capacity of aliphatic amines at C_5 which becomes effective after monosubstitution has taken place; *i.e.* the carbon atom at 8-position becomes more electronegative, which prevents the second nucleophilic attack to 8-position (Chart 1).

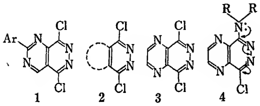


Chart 1

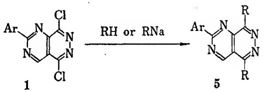
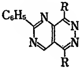
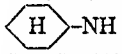
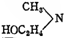
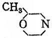
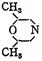
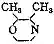
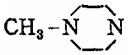
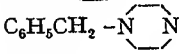
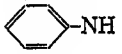
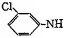
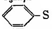
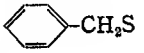


Chart 2

1) Part VI: S. Yurugi and M. Hieda, *Chem. Pharm. Bull.* (Tokyo), 20, 1522 (1972).
2) Location: *Jūso, Higashiyodogawa-ku, Osaka.*
3) S. Yurugi, M. Hieda, T. Fushimi, Y. Kawamatsu, H. Sugihara, and M. Tomimoto, *Chem. Pharm. Bull.* (Tokyo), 20, 1513 (1972).
4) S. Robinson and R.D. Haworth, *J. Chem. Soc.*, **1948**, 777.
5) J. Druey and B.H. Ringier, *Helv. Chim. Acta*, **34**, 195 (1951).
6) Y. Nitta, I. Matsuura, and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **13**, 586 (1965).
7) I. Matsuura and K. Okui, *Chem. Pharm. Bull.* (Tokyo), **17**, 2266 (1969).
8) N.R. Patel and R.N. Castle, *J. Heterocyclic Chem.*, **3**, 512 (1966).

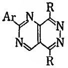
TABLE I. 2-Phenyl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (5)

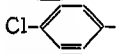
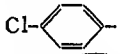
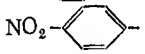
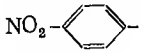
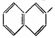
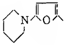
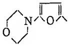


	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	C_3H_7NH	227—229	80.0	$C_{18}H_{22}N_6$	67.08	6.83	26.09	66.15	6.55	25.72
b	iso-C_3H_7NH	265	37.6	$C_{18}H_{22}N_6$	67.08	6.83	26.09	66.75	6.65	25.93
c	$CH_3OC_2H_4NH$	116—117	46.8	$C_{18}H_{22}O_2N_6$	63.88	6.55	24.84	61.10	6.30	24.07
d	$C_2H_5OC_2NH$	125—127	29.0	$C_{20}H_{28}O_2N_6$	62.80	6.85	21.98	62.45	6.78	21.96
e		223—226	68.5	$C_{24}H_{30}N_6$	71.61	7.51	20.88	71.65	7.69	20.81
f	$C_6H_5CH_2NH$	85—87	72.0	$C_{26}H_{22}N_6$	74.62	5.30	20.08	74.33	5.41	20.30
g		119—121	78.2	$C_{18}H_{22}O_2N_0$	61.02	6.22	23.73	60.50	6.16	23.47
h		141—142	80.0	$C_{20}H_{22}N_0$	69.34	6.40	24.26	68.52	6.46	23.77
i		144	80.0	$C_{22}H_{28}N_0$	70.56	7.00	22.44	70.26	7.03	22.30
j		180—182	90.0	$C_{20}H_{22}N_8O_2$	63.47	5.86	22.21	63.49	6.02	22.23
k		165—167	68.0	$C_{22}H_{26}O_2N_6$	65.02	6.40	20.69	65.30	6.38	20.64
l		209—212	43.0	$C_{24}H_{30}O_2N_6$	66.33	6.95	19.34	65.98	6.93	19.26
m		149—153	64.0	$C_{24}H_{30}O_2N_6$	66.33	6.95	19.34	66.55	6.99	19.21
n		152—154	73.0	$C_{20}H_{28}N_8$	63.16	7.37	27.74	64.49	6.89	27.10
o		181—182	20.0	$C_{34}H_{36}N_8$	73.35	6.52	20.13	73.50	6.41	19.92
p		198—200	68.0	$C_{22}H_{22}N_6S_2$	58.54	5.37	20.49	58.25	5.28	20.33
q		219—221	55.3	$C_{30}H_{26}N_6$	76.60	5.53	17.87	61.68	4.19	16.64
r		273	85.2	$C_{24}H_{18}N_8$	73.83	4.65	21.53	73.58	4.49	21.40
s		127—128	84.3	$C_{24}H_{10}N_6Cl_2$	62.75	3.51	18.30	61.93	3.58	17.44
t	N_3	214—216	97.0	$C_{12}H_8N_{10}$	49.66	2.07	48.28	49.53	2.35	48.01
u	CH_3O	204—206	93.0	$C_{14}H_{12}O_2N_4$	62.76	4.48	20.80	62.65	4.53	21.04
v	HS	269—272	100	$C_{12}H_8N_4S_2$	52.94	2.94	20.59	49.82	2.59	19.19
w	CH_3S	174—176	92.0	$C_{14}H_{12}N_4S_2$	56.00	4.00	18.67	55.52	4.03	18.63
x	C_3H_7S	103—105	89.2	$C_{18}H_{20}N_4S_2$	60.66	5.66	15.72	60.93	5.66	15.77
y		209—212	100	$C_{24}H_{16}N_4S_2$	67.92	3.80	13.20	67.86	3.63	13.18
z		189—192	87.7	$C_{26}H_{20}N_4S_2$	68.17	4.58	12.72	67.93	4.46	12.81

However, the reaction of **1** with excess of aliphatic amines under heating over 100° gave the corresponding 2-aryl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (**5**) in high yields. The reaction also proceeded under milder conditions, *e.g.* by refluxing with amines in ethanol, or even under room temperature in the case of the reaction with potassium hydrosulfide and sodium mercaptan. A variety of 2-phenyl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (**5**)

Table II. 2-Aryl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (**5**)



	Ar	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
A		iso-C_3H_7NH	273—274	66.0	$C_{19}H_{24}N_6$	67.86	7.14	25.00	67.92	7.11	25.41
B			226—228	70.0	$C_{23}H_{28}N_6HCl$	65.02	6.83	19.79	64.24	6.87	19.78
C			160—162	74.0	$C_{21}H_{22}O_2N_6$	64.29	6.12	21.43	64.31	6.20	21.45
D		N_3	214—216	97.0	$C_{13}H_8N_{10}$	51.32	2.63	46.05	51.32	2.52	46.15
E			180—181	40.6	$C_{22}H_{25}N_6Cl$	64.62	6.16	20.55	64.45	6.20	20.50
F			216—217	37.8	$C_{20}H_{21}O_2N_6Cl$	58.18	5.13	20.36	57.88	5.34	20.22
G			221—223	51.3	$C_{22}H_{25}O_2N_7$	62.99	6.01	23.73	62.90	6.21	23.10
H			269—270	50.8	$C_{20}H_{21}O_4N_7$	56.73	5.00	23.16	56.63	4.82	23.28
I			216—218	40.0	$C_{24}H_{24}O_2N_6$	67.28	5.65	19.63	67.22	5.69	19.51
J			133	24.0	$C_{21}H_{25}N_7$	67.17	6.71	26.12	67.25	6.51	26.52
K			197	46.0	$C_{19}H_{21}O_2N_2\cdot{}^1/_2H_2O$	58.59	5.58	25.70	58.98	5.58	25.70
L			158—159	52.6	$C_{20}H_{24}N_6S$	63.14	6.36	22.09	63.31	6.35	21.59
M			200—203	57.5	$C_{19}H_{20}O_2N_6S\cdot H_2O$	53.72	5.51	20.89	53.66	5.55	20.95
N			185	32.0	$C_{25}H_{33}ON_7\cdot{}^1/_2H_2O$	65.76	7.50	21.47	65.69	7.37	21.46
O			222	66.5	$C_{22}H_{27}O_4N_7$	58.28	6.00	21.62	58.03	5.96	21.57

and 2-aryl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (**5**) was synthesized by those methods expecting pharmacological activities. The resulting compounds are listed in Table I and Table II.

Among those compounds 2-phenyl-5,8-bis(substituted thio)pyrimido[4,5-*d*]pyridazines (**5w**, **5x**, and **5z**) were synthesized by alkylation of 2-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]-pyridazine-5,8-dithione (**5v**) with alkyl halide. 2-Aryl-5,8-diazidopyrimido[4,5-*d*]pyridazines (**5t** and **5D**) were obtained by reaction of **1** with sodium azide in dimethylsulfoxide under cooling. It has been reported that one of the azide group in 3,6-diazidopyridazine[9] and 5,8-diazidopyrazino[2,3-*d*]pyridazine[10] exist in the form of tetrazolopyridazine structure. Therefore one of the azide groups in **5t** and **5D** is expected to cylize with pyridazine ring to form tetrazole ring. Two possible structures for the cyclized product can be proposed, namely 6-azido-9-phenylpyrimido[4,5-*d*]tetrazolo[4,5-*b*]pyridazine (**6**) and 6-azido-8-phenylpyrimido-[4,5-*d*]tetrazolo[4,5-*b*]pyridazine (**7**). The nuclear magnetic resonance (NMR) spectra of **5t** and **5D** showed a signal of ring proton (H_4) at 4-position as a singlet, which indicated that each product consisted of single compound. When **5t** was heated with tetraline, a product (8a) which has one amino group in place of azido group was obtained, and the reaction of **5t** with sodium methoxide gave a monomethoxy compound (**8b**). In the IR spectrum of those products the absorption band due to azido group, which was observed at 2130 cm^{-1} in **5t** and **5D**, disappeared. This implies that another azido group which did not participate in the reaction had been cyclized to tetrazole ring.

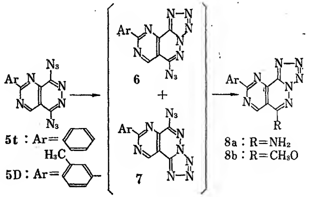


Chart 3

In the NMR spectrum of **8b**, the nuclear Overhauser effect (NOE) of 13.8% was observed between methyl protons of methoxy group and ring proton at 4-position. From these results the structure of **8b** was assigned as 6-methoxy-9-phenylpyrimido[4,5-*d*]tetrazolo[4,5-*d*]pyridazine. Therefore the parent compound (**5t**) was assigned as **6** (Ar=phenyl) (Chart 3).

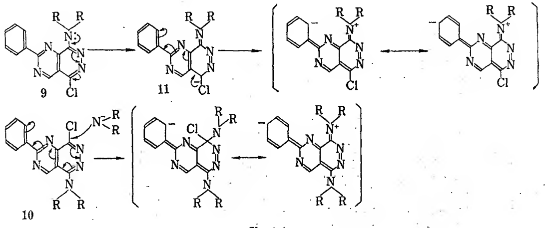


Chart 4

9) T. Itai and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **11**, 348 (1963).
10) L. DiStefano and R.N. Castle, *J. Heterocyclic Chem.*, **5**, 109 (1968).

As described above the nucleophilic disubstitution of 2-aryl-5,8-dichloropyrimido[4,5-*d*]-pyridazine (**1**) was found to proceed quite smoothly probably because of the effect by the aryl group at 2-position. It has already been mentioned in the preceding paper that a mixture of monosubstituted compounds which consists of nearly equal amount of 5- and 8-amine (**9** and **10**) was obtained when the reaction of **1** with amines was stopped halfway.[1] Therefore the assisting effect of the phenyl group is considered to work on the further substitution reaction of both **9** and **10**. In the compound **9**, 5-position is supposed to be an unfavorable position for the nucleophilic attack because of the electron donating effect of the amino nitrogen at 8-position leading to the structure like (**11**). The resonance effect of the 2-phenyl group, however, would be instrumental in delocalizing the electron at 5-position, which assists the nucleophilic attack. On the other hand in the case of **10**, the resonance effect of the phenyl group makes 8-position electron-poor, which would assist the nucleophilic attack overcoming the reverse effect by the amine nitrogen at 5-position.

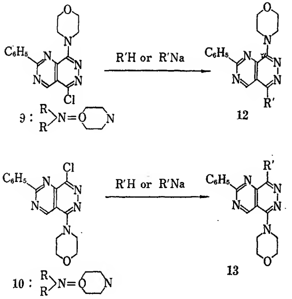


Chart 5

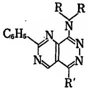
2-Phenyl-5,8-disubstitutedpyrimido-[4,5-*d*]pyridazines (**12** and **13**) which have different substitutents at 5- and 8-position were obtained by the reaction of 2-phenyl-5-chloro-8-morpholinopyrimido[4,5-*d*]-pyridazine (**9**, $\frac{R}{R}$>N: morpholino) and 2-phenyl-5-morpholino-8-chloropyrimido-[4,5-*d*]pyridazine (**10**, $\frac{R}{R}$>N: morpholino)[1] with nucleophiles such as piperidine, sodium ethoxide and sodium hydroxide. Their physical data and yields is presented in Tables III and IV.

2-Phenyl-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyridazine-5,8-dithione (**5v**) which was obtained by reaction of **1** with potassium hydrosulfide (Table I) could alternatively be prepared by reaction of 2-phenyl-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyridazine-5,8-dione (**14**)[3] with phosphorus pentasulfide in pyridine. **5v** was recognized to exist in thiolactam form in solid state by infrared (IR) spectrum (3125, 1563, 1553, and 1240 cm^{-1} in Nujol). The treatment of **5v** with methyliodide, propylbromide, and benzylchloride in alkaline solution gave the corresponding 2-phenyl-5,8-bis(substituted thio)pyrimido[4,5-*d*]pyridazine (**5w**, **5x**, and **5z**). 2-Phenyl-5,8-bis(phenylthio)pyrimido[4,5-*d*]-pyridazine (**5y**) was obtained by the reaction of **1** with sodium thiophenolate.

Although attempts to oxidize 2-phenyl-5,8-bis(substituted thio)pyrimido[4,5-*d*]pyridazines (**5**) expecting the formation of the corresponding sulfoxide or sulfone were made, no expected compounds were obtained. When the 5,8-bis(substituted thio) compounds (**5w**, **5x**, **5y**, and **5z**) and the 5,8-dithione compound (**5v**) were treated with chlorine as oxidizing agent, 2-phenyl-5,8-dichloropyrimido[4,5-*d*]pyridazine (**1**, Ar: phenyl) was obtained (Chart 5). Similar results have also been reported related to the displacement reaction of mercapto or substituted thio groups by chlorine in other heterocyclic systems.[11,12] This method may be useful as an alternative route for the preparation of **1**.

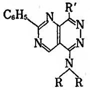
11) G.S. Shidhn, S. Naqui, and D.L. Lyengar, *J. Heterocyclic. Chem.*, **3**, 158 (1966).
12) C.W. Noell and R.K. Robins, *J. Am. Chem. Soc.*, **81**, 5997 (1959).

TABLE III. 2-Phenyl-5,8-disubstitutedpyrimodo[4,5-*d*]pyridazine (12)



R_2N-		R'	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a			156—158	65	$C_{21}H_{24}ON_6$	67.02	6.38	22.34	67.05	6.52	22.10
b		C_2H_5O	156—157	60	$C_{18}H_{19}O_2N_5$	64.10	5.64	20.77	64.41	5.58	20.96
c		HO	>305	70	$C_{16}H_{15}O_2N_5$	62.14	4.85	22.65	62.12	4.92	22.85

TABLE IV. 2-Phenyl-5,8-disubstitutedpyrimido[4,5-*d*]pyridazine (13)



R_2N-		R'	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a			159—161	52	$C_{21}H_{24}ON_6$	67.02	6.38	22.34	67.06	6.49	22.13
b		C_2H_5O	143—144	60	$C_{18}H_{19}O_2N_5$	64.10	5.64	20.77	63.75	5.62	20.85
c		HO	303—305	84	$C_{16}H_{15}O_2N_5$	62.14	4.85	22.65	62.19	4.63	22.84

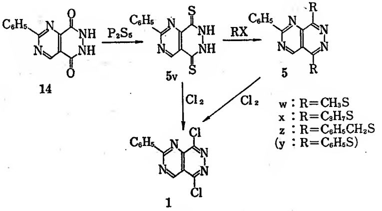


Chart 6

Experimental

2-Phenyl-5,8-disbsutitutedpyrimido[4,5-*d*]pyridazine (5) (Table I and Table II)——The general procedure is as follows: a) A mixture of 2-aryl-5,8-dichloropyrimido[4,5-*d*]pyridazine (1) (1.0 g) and aliphatic amines (10 g) was heated at 100—150° for 4—8 hr. After removal of the excess amine *in vacuo*, H_2O (about 100 ml) was added to the residue. The resulting crystals were filtered and recrystallized from EtOH to give **5**.

b) A solution of **1** (1.0 g) and arylamines (4 mole eq.) in EtOH (50 ml) was refluxed for 1 hr. After evaporation of the solvent, H_2O (about 100 ml) was added to the residue. The resulting solid was filtered and recrystallized from the appropriate solvent such as EtOH, AcOEt, and ether to give **5**.

c) To a solution of MeONa prepared from Na (460 mg) and MeOH (50 ml) was added the dichloride (1) (10 mmole) and the mixture was refluxed for 2—4 hr. After evaporation of the solvent *in vacuo*, H_2O (about 100 ml) was added to the residue. The resulting crystals were filtered and recrystallized from MeOH to give 2-phenyl-5,8-dimethoxypyrimido[4,5-*d*]pyridazine (**5u**).

d) To 10% KSH–EtOH (500 ml) was added the dichloride (**1**) (3.0 g) and the mixture was stirred for 5 hr under room temperature. After standing overnight, the solvent was evaporated *in vacuo*. The residue was dissolved in H_2O and the undissolved substance was removed by filtration. The filtrate was acidified was acidified with conc. HCl to yiel crystals, filtration and recrystallization of which from MeOH gave 2-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dithione (**5v**). IR (in Nujol) cm^{-1}: 3125 (NH), 1563, 1553 (CSNH), 1240 (C=S).

e) The dichloride (1) (1.0 g) was suspended in MeOH (200 ml) with stirring under room temperature and to the suspension was added the solution of sodium thiophenolate in MeOH (containing 2.5 mole equivalents of thiophenol). After stirring for 3 hr, the solvent was removed *in vacuo*. H_2O was added to the residue to yield yellow crystals which were filtered and washed with H_2O several times. Recrystallization from AcOEt gave 2-phenyl-5,8-bis(phenylthio)pyrimido[4,5-*d*]pyridazine (**5y**) as yellow needles (1.5 g).

2-Phenyl-5,8-bis(alkylthio)pyrimido[4,5-*d*]pyridazine (5w, 5x and 5z) (Table I)——To a solution of 2-phenyl 5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dithione (**5v**) (1 mmole) in 10% NaOH was added alkylhalide (CH_3J, C_3H_7Br and $C_6H_5CH_2Cl$) (2 mmole) with stirring under room temperature or at 50—60° for 3 hr. The resulting crystals were filtered and recrystallized from EtOH to give the corresponding 5,8-bis(alkylthio) compounds (**5x, 5y, and 5z**) as yellow needles.

6-Azido-9-arylpyrimido[4,5-*d*]tetrazolo[4,5-*b*]pyridazine (5t and 5D) (Table I and Table II)——The general procedure is as follows: DMSO (60 ml) was added to a mixture of the dichloride (1, Ar=phenyl, 3-tolyl) (3.0 g) and NaN_3 (2 mole eq.) with stirring under cooling. After stirring at room temperature overnight, the reaction mixture was poured into H_2O. The resulting crystals were collected by filtration and recrystallized from $CHCl_3$ to give **5t** and **5D** as cololess granules. Physical data of **5t** is as follows: IR (in Nujol) cm^{-1}: 2150 (N_3). NMR (in d_6-DMSO) τ: −0.10 (1H, singlet, ring proton), (in CF_3COOD): −0.47 (1H, singlet, ring proton).

6-Amino-9-phenylpyrimido[4,5-*d*]tetrazolo[4,5-*b*]pyridazine (8a)——A mixture of **5t** and tetraline (10 ml) was heated at 160° for 5 hr. After cooling, the resulting crystals were collected by filtration and recrystallized from THF gave **8a** (0.5 g, 47%), mp 218—219°. IR (in Nujol) cm^{-1}: 3300, 3460 (NH). An absorption band of azido group at 2150 cm^{-1} in the starting material (5_t) disappeared. *Anal.* Calcd. for $C_{12}H_8N_8$: C, 54.55; H, 3.03; N, 42.42. Found: C, 54.63; H, 2.97; N, 42.70.

6-Methoxy-9-phenylpyrimido[4,5-*d*]tetrazolo[4,5-*b*]pyridazine (8b)——To a solution of sodium methoxide prepared from Na (100 mg) and MeOH (50 ml) was added **5t** (1.0 g), and the mixture was refluxed for 3 hr. After evaporation of the solvent *in vacuo*, H_2O (about 100 ml) was added to the residue to give crystals, which were filtered and recrystallized from THF to give **8b** (0.8 g), mp 241—242°. The absorption band at 2150 cm^{-1} (N_3) in 8_t disappeared. NMR (in d_6-DMSO) τ: −0.19 (1H, singlet, ring proton). NOE (in d_6-DMSO, 100 Mc): NOE (13.8%) was observed between the ring proton (0.21 τ) and the methyl protons of methoxy group at 5-position (5.68 τ). *Anal.* Calcd. for $C_{13}H_9ON_7$: C, 55.91; H, 3.23; N, 35.13. Found: C, 56.10; H, 3.26; N, 35.23.

2-Phenyl-5-piperidino-8-morpholinopyrimido[4,5-*d*]pyridazine (12a) and 2-Phenyl-5-morpholino-8-piperidinopyrimido[4,5-*d*]pyridazine (13a) (Table III and Table IV)——The general procedure is as follows: The monosubstituted compound (9 and **10**, $\genfrac{}{}{0pt}{}{R}{R}\rangle N$: morpholino) (0.5 g) was heated with piperidine (5 ml) at 140—150° for 4—6 hr. After removal of excess amine, H_2O (about 50 ml) was added to the residue. The resulting crystals were collected by filtration and recrystallized from EtOH to give the corresponding disubstituted product (12a and 13a).

2-Phenyl-5-ethoxy-8-morpholinopyrimido[4,5-*d*]pyridazine (12b) and 2-Phenyl-5-morpholino-8-ethoxypyrimido[4,5-*d*]pyridazine (13b) (Table III and Table IV)——The general procedure is as follows: To a solution of EtONa prepared from Na (230 mg) and EtOH (50 ml) was added the monosubstituted compound (9 and 10, $\genfrac{}{}{0pt}{}{R}{R}\rangle N$: morpholino) (10 mmole) and the solution was refluxed for 1 hr. After evaporating the solvent, H_2O (about 200 ml) was added to the residue to give crystals, which were filtered and recrystallized from EtOH to give the corresponding disubstituted product (**12b** and **13b**).

2-Phenyl-5,6-dihydro-8-morpholinopyrimido[4,5-*d*]pyridazin-5-one (12c) and 2-Phenyl-5-morpholino-7,8-dihydropyrimido[4,5-*d*]pyridazin-8-one (13c)——The general procedure 8i as follows: The monosubstituted compound (9 and 10; $\genfrac{}{}{0pt}{}{R}{R}{>}N$: morpholino) (0.3 g) was refluxed with a mixture of 10% NaOH (3 ml) and EtOH (30 ml) for 5 hr. After evaporation of the solvent, H_2O (about 50 ml) was added to the residue. H_2O (about 50 ml) was added to the residue. An indissolved substance was removed by filtration and the filtrate was acidified with dil. HCl to yield crystals, which were filtered and recrystallized from dioxane to give the corresponding disubstituted product (12c and 13c). IR (in Nujol) cm^{-1}: 1650 (CONH) in both products.

2-Phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dithione (5v)——To a mixture of 2-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyridazine-5,8-dione (14) (1.2 g) and pyridine (50 ml) was added P_2S_5 (2.22 g) under reflux with stirring and the stirring was continued under reflux for 1 hr. After cooling, the solvent was evaporated *in vacuo* and the residue was poured into ice-water (50 ml). The resulting solution was heated on water bath for 2 hr. After cooling, the solution was filtered and the filtrate was adjusted to pH 2 with conc. HCl. The above procedure was repeated twice on the resulting precipitates and the precipitates were refluxed with 95% EtOH for 1.5 hr. The resulting crystals were collected by filtration to give to give 5v as reddish orange granules (180 mg, 14%), mp 269—272°. The structure of this substance was confirmed by comparing its infrared spectrum (in Nujol) with that of authentic sample.

2-Phenyl-5,8-dichloropyrimido[4,5-*d*]pyridazine (1)——a) 2-Phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]-pyridazine-5,8-dithione (5v) (1.0 g) was suspended in a mixture of AcOH (20 ml) and H_2O (1.2 ml) and chlorine gas was bubbled into the suspension under cooling for 2 hr. After excess chlorine was removed by passing N_2 to the solution, the solution was poured into ice-water (100 ml) with stirring. The resulting crystals were filtered to give the dichloride (1) (1.02 g, 68.5%), mp 211—213°. *Anal.* Calcd. for $C_{12}H_6N_4Cl_2$: C, 51.99; H, 2.17; N, 20.22; Cl, 25.49. Found: C, 52.22; H, 2.06; N, 20.57; Cl, 25.49. IR spectrum (in Nujol) of this substance showed complete identity with authentic sample.

b) To a solution of 2-phenyl-5,8-bis(methylthio)pyrimido[4,5-*d*]pyridazine (5w) (1.5 g) in $CHCl_3$ (50 ml) was passed chlorine gas under cooling for 2 hr. After evaporation of the solvent and excess chloride *in vacuo*, the dichloride (1) was obtained as crystalline residue (1.28 g, 70.3%). This substance was identified by comparing its IR spectrum (in Nujol) with that of authentic sample. 2-Phenyl-5,8-bis(substituted thio)-pyrimido[4,5-*d*]pyridazines (5x, 5y, and 5z) were treated just in the same manner as described above to give the dichloride (1) in following yields: 5x ($R=C_3H_6S$), 54%; 5y ($R=C_6H_5S$), 78%; 5z ($C_6H_5CH_2S$), 70%.

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